Kif3a constrains beta-catenin-dependent Wnt signalling through dual ciliary and non-ciliary mechanisms.

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Public Summary:

Scientific Abstract:
Primary cilia are microtubule-based organelles involved in signal transduction and project from the surface of most vertebrate cells. Proteins that can localize to the cilium, for example, Inversin and Bardet-Biedl syndrome (BBS) proteins, are implicated in both beta-catenin-dependent and -independent Wnt signalling. Given that Inversin and BBS proteins are found both at the cilium and elsewhere in the cell, the role of the cilium itself in Wnt signalling is not clear. Using three separate mutations that disrupt ciliogenesis (affecting Kif3a, Ift88 and Ofd1), we show in this study that the primary cilium restricts the activity of the canonical Wnt pathway in mouse embryos, primary fibroblasts, and embryonic stem cells. Interestingly, unciliated cells activate transcription only in response to Wnt stimulation, but do so much more robustly than ciliated cells. Loss of Kif3a, but not other ciliogenic genes, causes constitutive phosphorylation of Dishevelled (Dvl). Blocking the activity of casein kinase I (CKI) reverses this constitutive Dvl phosphorylation and abrogates pathway hyper-responsiveness. These results suggest that Kif3a restrains canonical Wnt signalling both by restricting the CKI-dependent phosphorylation of Dvl and through a separate ciliary mechanism. More generally, these findings reveal that, in contrast to its role in promoting Hedgehog (Hh) signalling, the cilium restrains canonical Wnt signalling.